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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,212	12/11/2003	Donald W. Kufe	00530-095002 / 718.09	7998

26211 7590 03/03/2008
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EXAMINER	
HILL, KEVIN KAI	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
03/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/733,212	KUFE, DONALD W.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *2-4,6,10-12 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, 7-9, 13 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 12, 2007 has been entered.

Applicant has elected without traverse the invention of Group I, claims 1-8, drawn to a method of identifying a compound that inhibits binding of MUC1 to a tumor progressor. Applicant elected the tumor progressor species β-catenin (claim 5).

Amendments

In the reply filed December 12, 2007, Applicant has withdrawn claims 2-4, 6, 10-12 and 14, amended claims 1 and 9, and added new claims, Claims 17-18.

Claims 2-4, 6, 10-12 and 14 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1, 5, 7-9, 13 and 15-18 are under consideration.

Priority

Applicant's claim for priority under 35 U.S.C. 119(e) or 120 regarding the parent provisional application 60/257,590, filed on December 22, 2000 and provisional application 60/308,307, filed on July 27, 2001 is acknowledged.

The effective priority date of the instant application is granted as December 22, 2000.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the December 12, 2007 response will be addressed to the extent that they apply to current rejection(s).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. **Claims 1, 5, 7-9, 13 and 15-18 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Brent et al (U.S. Patent No. 6,004,746; *of record) in view of Li et al (Mol. Cell Biol. 18(12): 7216-7224, 1998, * of record in IDS), Yamamoto et al (J. Biol. Chem. 272(19): 12492-12494, 1997; *of record), and Zrihan-Licht et al (FEBS Letters 356(1):130-136, 1994).

Determining the scope and contents of the prior art.

Brent et al disclose methods for identifying compounds that are agonists or antagonists of protein interactions, the method comprising determining whether a first protein test agent is capable of physically interacting with a second protein test agent (Abstract; col. 6, lines 5-15). Antagonists that inhibit the binding of the first test agent to the second test agent may be readily identified and isolated, wherein once a protein-protein interaction between the first and second

test agents has been recorded, a candidate antagonist is introduced and the result is measured (col. 7, line 57- col. 8, line 39). Interaction antagonists are useful as models to design simple mimetics (col. 8, lines 7-8). Candidate antagonist compounds may be proteinaceous, e.g. peptides or polypeptides, or non-proteinaceous. Brent et al disclose, for example, the identification of Cdk2-interacting peptide aptamers, wherein Brent et al suggest that these peptide aptamers may be used in competition experiments (col. 18, lines 29-34). Brent et al disclose that the inventive method may be performed intracellularly or in cell-free systems (col. 8, lines 24-25; col. 21, lines 33-34; col. 22, lines 30-33).

Brent et al disclose that the "bait" first protein test agent and "prey" second protein test agent may be chosen from any protein of interest, including proteins of unknown, known or suspected therapeutic or pharmacological importance such as oncoproteins or the cytoplasmic portions of membrane-associated receptors, or signaling proteins (col. 10, lines 38-50).

Brent et al do not explicitly disclose MUC1 or beta-catenin as first and second test agents to be tested in the assay. However, at the time of the invention, Li et al taught a method of identifying a compound that inhibits binding of MUC1 to the β-catenin tumor progressor, the method comprising the step of providing a MUC1 test agent comprising a YEKV site, providing a β-catenin test agent that binds to the MUC1 test agent, and contacting the MUC1 test agent with a test compound that is GSK-3β, wherein the GSK-3β test compound inhibits the binding of MUC1 to β-catenin (pg 7220, Figure 4).

Li et al also taught a method of identifying a compound that inhibits binding of MUC1 to the β-catenin tumor progressor, the method comprising the step of providing a MUC1 test agent comprising a YEKV site, providing a β-catenin test agent that binds to the MUC1 test agent, and contacting the MUC1 test agent with a β-catenin test agent in the presence of a test compound that is GSK-3β, wherein the contacting occurs in a cell, wherein the GSK-3β test compound inhibits the binding of MUC1 to β-catenin (pg 7220, Figure 5).

Li et al taught that GSK-3β binds directly to an STDRSPYE site of SEQ ID NO:1 in the cytoplasmic domain of the human MUC1 (see pg 7218, Figure 2), wherein amino acids YE are the first two amino acids of the YEKV site (SEQ ID NO:11). Phosphorylation of MUC1 by GSK-3β decreases binding of MUC1 to β-catenin *in vitro* and *in vivo*. Li et al taught that signals

other than GSK-3β-mediated phosphorylation may contribute to regulation of the MUC1-β-catenin complex (pg 7222, col. 1). The site in MUC1 for GSK-3β binding and phosphorylation is adjacent and joined to the β-catenin binding site by the YEKV motif (Figure 2A). Li et al suggest that the association of GSK-3β with MUC1 may displace β-catenin, and teach that GSK-3β inhibits the association of MUC1 and β-catenin *in vitro* and *in vivo* (pg 7222, col. 1). Li et al taught the use of a peptide aptamer to block the interaction between a MUC1 test agent and a GSK-3β test agent (pg 7218, Figure 2C), as well as the step of determining whether the MUC1 test agent is phosphorylated at a specific amino acid site (pg 7219, Figure 3).

Similarly, Yamamoto et al taught a method of identifying a compound that inhibits binding of MUC1 to the β-catenin tumor progressor, the method comprising providing a MUC1 test agent comprising a YEKV site (SEQ ID NO:11), providing a β-catenin tumor progressor test agent, contacting the MUC1 test agent with the β-catenin test agent in the presence of a test compound, wherein the contacting occurs *in vitro*, and determining whether the test compound inhibits binding of MUC1 to β-catenin (pg 12493, Figure 4).

Neither Brent et al, Li et al nor Yamamoto et al disclose the step of determining whether the test compound inhibits phosphorylation of the YEKV site of the MUC1 test agent. However, at the time of the invention, those of ordinary skill in the art were skilled in methods to determine whether a substrate is or is not phosphorylated (see Li et al regarding serine phosphorylation). For example, Zrihan-Licht et al taught that the cytoplasmic domain of MUC1 comprising SEQ ID NO:1 is extensively phosphorylated on tyrosine residues, wherein the art recognizes that phosphorylation on tyrosine residues is a key step in signal transduction pathways mediated by membrane proteins, e.g. MUC1. Zrihan-Licht et al demonstrate the ability to detect tyrosine phosphorylation of a MUC1 test agent (Zrihan-Licht et al, pg 132, Figure 1).

Ascertaining the differences between the prior art and the claims at issue.

The cited prior art does not teach the test compound is a peptide fragment of the second test agent, e.g. the β-catenin tumor progressor. However, Brent et al disclose the use of peptide aptamers, wherein these peptide aptamers may be used in competition experiments (col. 18, lines

29-34). Absent evidence to the contrary, nothing non-obvious is seen with the recited limitation that the test compound is a peptide fragment [aptamer] of the second test agent, e.g. β-catenin, because it is well within the skill of the artisan to design peptide fragments of either the first or second test agents to compete for the corresponding binding site in the second or first test agent, respectively.

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals including medical doctors, scientists, or engineers possessing advanced degrees such as M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, biochemistry, and signal transduction. Therefore, the level of ordinary skill in this art is high.

At the time of the invention, the ordinary artisan knew and practiced methods to detect and identify protein-protein interaction domains, antagonists thereof, and how to determine whether or not a specific amino acid motif is phosphorylated, e.g. tyrosine phosphorylation, under a given condition.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to try a method to identify a compound that inhibits the binding between MUC1 and a tumor progressor test agent such as β-catenin, wherein the compound inhibits the phosphorylation of the YEKV (SEQ ID NO:11) site of the MUC1 test agent, and thereby inhibits the binding of MUC1 to the β-catenin tumor progressor test agent because "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense."

At the time of the invention, those of ordinary skill in the art were already aware that:

i) the MUC1 cytoplasmic domain possessed a peptide motif that mediates binding to β-catenin,

ii) the MUC1 cytoplasmic domain possessed a peptide motif that mediates binding to GSK-3β,

iii) GSK-3β decreases binding of MUC1 to β-catenin *in vitro* and *in vivo*,

iv) the YEKV (SEQ ID NO:11) peptide motif is situated between the MUC1 peptide motif to which GSK-3β binds and the MUC1 peptide motif to which β-catenin binds, and

v) phosphorylation on tyrosine residues is a key step in signal transduction pathways mediated by membrane proteins, e.g. MUC1.

Thus, the YEKV peptide motif (SEQ ID NO:11) is situated at a location that one of ordinary skill in the art would reasonably expect to affect the binding of one or more MUC1-interacting proteins, e.g. GSK-3β and/or β-catenin, and there are only four possible outcomes regarding the effects of the YEKV peptide motif phosphorylation status:

1) tyrosine phosphorylation at YEKV promotes β-catenin binding to MUC1,

2) tyrosine phosphorylation at YEKV inhibits β-catenin binding to MUC1,

3) inhibition of tyrosine phosphorylation at YEKV promotes β-catenin binding to MUC1, and

4) inhibition of tyrosine phosphorylation at YEKV inhibits β-catenin binding to MUC1.

An artisan would be motivated to try a method to identify a compound that inhibits the phosphorylation of the YEKV (SEQ ID NO:11) peptide motif so as to inhibit the binding of MUC1 to β-catenin because: a) Li et al taught that modification of the serine in TDRSPYE by phosphorylation or mutation reduced, but did not completely eliminate, the interaction between MUC1 and β-catenin, and thus, signals other than GSK-3β-mediated phosphorylation may contribute to regulation of the MUC1-β-catenin complex (pgs 7221-7222, joining ¶), and b) Yamamoto et al taught that the cytoplasmic domain of MUC1 is phosphorylated on tyrosine, but that it is not known if tyrosine sites influence binding of catenins to the serine-rich motif (pg 12494, col. 1), thereby suggesting pursuit of this possible regulatory feature.

It also would have been obvious to one of ordinary skill in the art to use a test compound that is a peptide fragment of the second test agent, e.g. the β-catenin tumor progressor with a reasonable chance of success because the art recognized and practiced the ability to generate and use peptide aptamers (e.g. Brent et al) in methods of identifying antagonists of protein-protein

interactions. An artisan would be motivated to use a test compound that is a peptide fragment of β-catenin because whereas the β-catenin binding site on MUC1 is known, the MUC1 binding site on β-catenin is not known, and thus the artisan could gain new insights regarding the functional domains regulating the activity of the β-catenin tumor progressor molecule.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. **Claims 1, 5, 7-9, 13 and 15-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims 1, 5, 7-8 of copending Application No. 10/032,786 (U.S. 2002/0110841 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because the method in the co-pending application comprises the use of a MUC1 test agent that possesses SEQ ID NO:1 and SEQ ID NO:11 of the instant application, the tumor progressor agent is β-catenin, and wherein the assay measures an inhibition of phosphorylation of MUC1 so as to inhibit binding of MUC1 to β-catenin [0152, Example 5]. Thus, the method in the co-pending application reasonably embraces and is substantially similar to the method claimed in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

3. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Q. JANICE LI/

Primary Examiner, Art Unit 1633